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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,717	03/24/2004	Ka-Yiu San	61683-00005USPT	6585

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/808,717	SAN ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3 and 5-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0609/05 & 07/06/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to restriction requirement filed May 25, 2006 is acknowledged. Claim 1 has been amended; claims 1-26 are pending. Applicants elected invention VIII, claims 1-5 all in part directed to a method of manipulation of metabolism of a cell comprising elevated expression of a combination of three enzymes, pantothenate kinase, alcohol acetyl transferase and pyruvate dehydrogenase. Claims 1, 3 and 4 read on the elected combination of genes/enzymes and are under examination. Claims 2, 5-26 are withdrawn from examiner's consideration as directed to a non-elected invention; see 37 CFR 1.142(b).

Detailed Action

1. Election/restriction

Applicant's election with traverse of Group VIII in the reply filed on May 25, 2006 is acknowledged. The traversal is on the ground(s) that

1) there are 26 claims in the application, 9 of which are independent and the number of groups in restriction requirement is 27;

2) the examiner separated legitimate members of a Markush group, i. e.

pyruvate dehydrogenase

pyruvate formate lyase

pyruvate oxidoreductase

pantothenate kinase

phosphopentetheine adenyltransferase,

which are Markush group of "enzymes involved in A-CoA metabolism" ;

3) the enzymes listed under 2) are "related functionally as each metabolizes CoA or CoA derivatives";

4) the search of the field will not place an undue burden on the examiner.

This is not found persuasive. Regarding point 1) the number of groups in any restriction requirement does not depend on the number of claims or number of independent claims, but on the subject matter Applicant has chosen to be encompass in the claims.

Regarding point 2, MPEP §803.02 defines unity of invention to exist broadly where "*compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature essential to that utility.*" In the instant case, however, every of the enzymes listed by the original claim 2 has different enzymatic activity than any other and participates in a specific biochemical reaction, as well as has structure (amino acid sequence) which is unique. The phrase "a function of metabolizing CoA or CoA derivatives" does not define any common utility of the enzymes listed under 2). There are more than 100 different reactions in which CoA and one of its derivative, acetyl- CoA, to mention only one, participate (Vadali et al., Biotechnol. Prog. 20/3, 692-697, 2004, enclosed in the IDS).

As to the burden on the examiner, there are 16 combinations of two enzymes selected from the group of 5, and further three-enzyme combinations, four-enzyme combinations and the combination comprising all five enzymes still increase the number of combinations to be searched. This is a burden on examiner.

The requirement is still deemed proper and is therefore made FINAL.

2. Priority

Acknowledgment is made of Applicant's claim to the benefits of the provisional applications 60/457;093 and 60/457,635 filed 03/24/2003 and 03/26/2003, respectively. Priority of claims 1-5 as directed to the elected invention has been granted.

3. Rejections

3.1. 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 are directed to a method of manipulating the metabolism of a cell comprising elevated expression of one or more enzyme from the group of 8 and combination thereof. The claims are missing any steps and effects of the claimed method. It is unknown what might be the result of this manipulation, i.e. what might be the purpose of this manipulating.

Claims 1 and 4 are unclear in recitation "elevated expression of one or more enzymes involved in A-CoA metabolism". The phrase is confusing, as it is unclear

whether the cell "comprises elevated expression", or the method comprises elevating expression of one or more enzymes". For examination purposes the latter is assumed.

Claim 3 is rejected as depending on claim 2 that does not belong to the elected invention.

Claim 3 is rejected because the phrase "the cell expresses one of the group consisting of". The cells does not overexpress any "group"; the cells is to overexpress an enzyme that is selected from a group. The latter is assumed for examination.

Claim 3 has no antecedent in claim 1, because claim 1 does not recite a cell that expresses any enzyme or overexpresses any enzyme. In addition, the phrase is confusing, because it is unknown whether the cell overexpresses the recited genes before the manipulating the metabolism or after that. Claim 3 is also objected as depending on claim 2 that does not belong to the elected invention.

Claim 4 is additionally rejected because it recites the phrase "increasing the A-CoA flux in a cell" which is not defined by the claim or specification, thus one having skills in the art would not know how to measure the increase in the A–CoA flux. For examination purposes it is assumed that applicants mean the level of A-CoA, i.e., concentration, which was measured as presented in Example 8.

3.2. 35 USC section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.2.1. Written description

Claim 1,3and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is rejected for introducing new matter. Neither the original claims nor the specification disclose a manipulating of metabolism of a cell or increasing the A-CoA flux in a cell by elevating expression of pantothenate synthase (PanC) and aspartate 1-decarboxylase (PanD). The disclosure does not teach these enzymes and their rate limiting role in A-CoA synthesis. These enzymes have been entered to claim 1 in the amendment filed together with election of invention.

In addition, claims 1, 3 and 4 are rejected for lack of written description of a cell whose metabolism was manipulated, or the CoA flux in the cell was increased, by elevating expression of

a) pyruvate formate lyase

b) pyruvate oxidoreductase

c) phosphopentetheine adenyltransferase,

d) any alcohol acetyltransferase,

e) pyruvate oxidoreductase

f) pantothenate synthase, and

g) aspartate 1-decarboxylase, or

h) any combination thereof.

The specification teaches E. coli cells transformed with panK, ATF2 and pyruvate dehydrogenase genes separately, or in combination; see Table 2. The origin and sequences of genes used for manipulation are not described. Also, the disclosure does not provide written description of any cell that is to be transformed as broadly recited by the claims. The specification teaches E. coli cells transformed with panK, ATF2 and pyruvate dehydrogenase genes separately, or in combination; see Table 2. The panK gene is that of E.coli, the pyruvate dehydrogenase gene is not identified, and ATF2 gene is any gene ATF2 obtained form yeast. Thus, the description of the latter two genes is generic. There is an enormous number of organisms possessing pyruvate dhydrogenase and even grater number of muteins of that enzyme and its recombinant forms. Also, there are many wild type species of the genus of yeast and even greater number of mutated strains.

Manipulating of metabolism in E. coli cells by transforming it with panK, ATF2 and pyruvate dehydrogenase genes separately, or in combination does not characterize elevating expression of

a) pyruvate formate lyase

b) pyruvate oxidoreductase

c) phosphopentetheine adenyltransferase,

d) any alcohol acetyltransferase,

e) pyruvate oxidoreductase

f) pantothenate synthase, and

g) aspartate 1-decarboxylase, or

h) any combination thereof, in any cell.

As to claim 4, manipulating of metabolism in E. coli cells by transforming it with panK, ATF2 and pyruvate dehydrogenase genes, separately or in combination, does not provide for elevating expression of any enzyme which is involved in one or more rate limiting steps of A-CoA synthesis, absent teaching said enzymes and their encoding genes.

Furthermore, as to claim 4, the specification teaches that not every transformation with panK performed by Applicants resulted in an increase in the level of A-CoA. Fig. 5 definitely teaches a decrease in the level of A-CoA in DH10B(pRV380) strain. However, the data for DH10B(pRV380) strain presented in Fig. 6a teach an increase in acetyl CoA level. Thus, it is not clear whether transformation with panK alone indeed causes an increase in A-coA. Certainly the increase is caused by addition of pantothenic acid to the medium.

Furthermore, the origin and sequences of genes used for manipulation are not described. Applicants only teach that pan K gene is that of E.coli and ATF2 gene is a yeast gene. However, the latter is a generic description, because there are many wild type species of the genus of yeast and even greater number of mutated strains.

All together, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention at the time the application was filed.

3.2.2. Scope of enablement

Claim 1, 3, and 4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for elevating expression of panK of E.coli, and increasing activity of panK, does not reasonably provide enablement for elevating expression of panK, ATF2, and puruvate dehydrogenase (elected combination of enzymes) as well as any enzyme of subgenera of

a) pyruvate formate lyase,

b) pyruvate oxidoreductase,

c) phosphopentetheine adenyltransferase,

d) any alcohol acetyltransferase,

e) pyruvate oxidoreductase,

f) pantothenate synthase, and

g) aspartate 1-decarboxylase, or

h) any combination thereof in any cell.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered

in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breadth of the claims covers overexpressing any of the enzymes belonging to the above listed genera, including any natural and man-made enzyme (i.e., an astronomical number of enzymes) and any host cell.

While manipulating metabolism of cell by overexpressing enzymes is well developed and the skills of artisans high, not every gene encoding the enzymes listed generically above may be overexpressed in any cells. Genetic code usage is specific for the cell to be transformed. The host cells have also specific requirements as to the expression vector, i.e., plasmid and control expression elements it comprises. Providing for E. coli transformed with panK is not a sufficient guidance of the genus of genes and cells to be used by a skilled artisan to make the invention as claimed. Furthermore, applicants own data suggest, that without supplying the medium with the substrates of the overexpressed enzymes the overexpression alone is not enough for increasing the level of A-coA in the transformed cell (compare Fig. 5 and 6a).

Moreover, those skilled in the art realize that metabolic pathways of cells of every cell type are distinct, such that a showing of overexpression of a group of genes in one cell type leads to increased level of A-coA may not be true in other cell types as well.

In addition, both the genus of genes and the genus of cells to be transformed, encompass an extremely large number of species and there is no teaching by Applicants which gene, expression vector and cell to chose. In conclusion, one having skills in the art is forced to experimentation which has a low probability of success and is improperly extensive and undue.

3.3. 35 USC section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated Ka-Yiu San et al., (Metabolic Engineering through Cofactor Manipulation and Its Effects on Metabolic Flux Redistribution in *Escherichia coli*, Metabolic Engineering, February 27, 2002, 4, 182-192, included in the Information Disclosure Statement). The claims are directed to a method of manipulating the metabolism of a cell comprising elevating expression of enzymes that are involved in rate limiting steps of A-CoA synthesis, including the enzyme acetyltransferase 2. San et al. manipulated metabolism of E. coli cell by transformation it with alcohol acetyltransferase 2, causing overproduction of isoamylacetate isoamyl alcohol was added to the medium (Table 4). San et al. teach transformation of E. coli having overexpressed panK or wild type expression of panK;

see strains DV79 and DV62 description on page 190, left column under subtitle *Result and Discussion*, and Table 3, with ATF2 gene of S. cerevisiae. Transformation with only ATF2 gene cause production of isoamylacetate in wild type of E. coli, because the overexpression of acetyltransferase in the wild type causes increasing the flux of metabolites from CoA through A-CoA towards isoamyl acetate as illustrated in Fig. 6(b). (The left part of Fig. 6b of San et al is identical to let part of Fig. 1 of the instant application.) Sun et al teach also that overexpressing panK, caused even greater production of isoamylacetate in strain DV79, which was related by San et al to an increase in the pull of CoA; see the text under Table 4. Sun et al. anticipate the instant invention, because their article was published more than a year before the filing the provisional applications of the instant application.

In addition, claims 1 and 3 are rejected over Rock et al. (Pantothenate Kinase Regulation of the Intracellular Concentration of Coenzyme A, J. Biol. Chem. 2000, 275, 1377-1383; copy enclosed). Rock et al. disclose that transformation of Cos-7 cells with panK gene not only increases cellular activity of PanK (Fig. 4) but also the cellular pull of CoA (Fig. 6). Thus Rock et al. disclose the method of claims 1 and 3.

3.4. 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over San et al., quoted in the above rejection under 35 USC 102(b) in view of Rock C. O. et al. (Pantothenate Kinase Regulation of the Intracellular Concentration of Coenzyme A. J. Biol. Chem. 2000, 275, 1377-1383, enclosed).

The claim is directed to a method of increasing the A-CoA flux in a cell comprising elevating expression of one or more enzymes involved in A-CoA metabolism. Thus the scope of the claim reads on elevating expression of enzymes pantothenate kinase and alcohol acetyl transferase ATF2.

San et al. teach transformation of E. coli having overexpressed panK or wild type expression of panK; see strains DV79 and DV62 description on page 190, left column under subtitle *Result and Discussion*, and Table 3, with ATF2 gene of S. cerevisiae. Transformation with only ATF2 gene cause production of isoamylacetate in wild type of E. coli, because the overexpression of acetyltransferase in the wild type causes increasing the flux of metabolites from CoA through A-CoA towards isoamyl acetate as illustrated in Fig. 6(b). (The left part of Fig. 6b of Sun et al is identical to let part of Fig. 1 of the instant application.) Sun et al teach also that overexpressing panK, caused even greater production of isoamylacetate in strain DV79, which was related by San et al to an increase in the pull of CoA; see the text under Table 4. Sun at al do not teach transformation of E. coli with panK. However, Rock teaches that transformation of COS-7 cells with panK, causes an increase in the CoA pull, Fig. 6.

It would have been obvious for one having ordinary skills in the art to have a method of manipulating of metabolism of a cell as Sun did, and replace a cell having overexpressed panK gene, by a cells into which the pan K gene is introduced for elevating expression of the pantothenate kinase. The motivation is provided by Rock et al. who teach that panK is the rate-controling enzyme in CoA biosynthesis in E. coli; see the first paragraph in the right column, page 1377. Thus, one having intention of increasing the A-CoA flux in a cell would be motivated to overexpressed panK in the cell. The expectation of success was very high because Rock et al has shown overexpression of panK in a cell, and the art at the time of filing taught it was easy to transform E. coli with its own gene as the applicant did. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

2. Conclusion

Claims 1, 3 and 4 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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